REMARKS

Claims 1, 5-10, 12-14, 17, and 19 were pending and examined in the February 7, 2007 final Office Action. In this reply, claim 1 has been amended, and claims 12-14 cancelled. Accordingly, claims 1, 5-10, 17 and 19 will be pending upon entry of this amendment.

Specifically, claim 1 has been amended to cancel the new matter as suggested by the Examiner on page 4 of the Final Office Action dated February 7, 2007. Claim 1 now covers the use of the species of gp39 antibody that is produced by the deposited hybridoma 24-31. Support for this amendment is found at page 6, lines 19-25 of the specification as filed.

Rejection Under 35 U.S.C. § 112 - Written Description

The Examiner contends that claims 1, 5-10, 17, and 19 do not contain a written description of the claimed invention. Specifically, he argues that the phrase "wherein the anti-gp39 antibody or fragment binds to an epitope which is specifically bound by a monoclonal antibody produced by 24-31 hybridoma" is not supported by the specification as originally filed and thus, contains new matter. The Examiner suggests that this new matter be canceled in response to the Office Action. *See* Final Office Action dated February 7, 2007, pages 2-4.

Claim 1 has been amended by canceling the above-referenced phrase as suggested by the Examiner. It is respectfully submitted that this amendment overcomes the written description rejection as the new matter has been deleted from the claim. The claim now covers the species of anti-gp39 antibody that is produced by the 24-31 hybridoma which is fully described in the specification as filed at page 6, lines 19-25. Thus, claim 1 as amended, and claims 5-10, 17, and 19 which depend therefrom, are now sufficiently described so as to convey to one of skill in the art that the inventor had possession of the claimed invention.

Rejection under 35 U.S.C. § 112 - Enablement

The Examiner has also maintained his rejection to claims 12-14 as not being enabled under 35 U.S.C. § 112. It is respectfully submitted that the cancellation of these claims moots this rejection.

Rejection under 35 U.S.C. § 103 - Obviousness

The Examiner has maintained his rejection of claims 1, 5-10, 12-14, 17 and 19 as obvious in view of U.S. Patent No. 6,592,868 issued to Lederman *et al.* ("Lederman") in view of U.S. Patent No. 5,747,037 issued to Noelle ("Noelle"). The Examiner contends that presently pending claims are obvious in view of the Lederman '868 patent (which teaches the use of a CD40L-specific antibody for the treatment of diabetes) in combination with the disclosure in the Noelle '037 patent of monoclonal antibody 24-31.

This rejection is respectfully traversed.

The cited references, either alone or in combination, do not teach or suggest all of the limitations of the presently pending claims. Specifically, the references do not teach or suggest "a method of preventing *T cell mediated* tissue destruction associated with type I diabetes .. wherein .. tissue destruction results from a *T cell mediated immune reaction* to autoantigen." Moreover, for the reasons set forth below, a person of skill in the art would not have had a reasonable expectation of success in using the claimed method for treating the T cell mediated immune reactions and tissue destruction in type I diabetes based upon the teachings of these references. Thus, the Examiner has not set forth a *prima facie* case of obviousness.

As acknowledged by the Examiner, Lederman is limited to inhibiting B cell activation in autoimmune diseases, not T cell-mediated autoimmune diseases, as shown by the passage at column 10, line 62 to column 11, line 7 (emphasis added):

> This invention provides a *method of inhibiting B cell activation* to an animal which comprises administering to the animal an effective inhibiting amount of a pharmaceutical composition comprising the monoclonal antibody which specifically recognizes the activated T cell surface protein and a pharmaceutically acceptable carrier. For the purposes of this invention, an "effective inhibiting amount" of a pharmaceutical composition is any amount of the pharmaceutical composition which is effective to bind to a protein on the surface of the activated T cells and thereby *inhibit T cell activation of B cells*. In one embodiment of this invention, the B cells are resting B cells. In another embodiment of this invention, the B cells are primed B cells.

There is no additional teaching in Lederman that would expand the scope of his disclosure to anything more than a method of inhibiting B cell activation because Lederman discloses only that *CD40L antagonists target helper T cell/ B cell interactions, not T cell-mediated immunological responses*. *See* Declaration of Clark, ¶¶ 18 and 19.

Furthermore, the Lederman '868 patent mentions diabetes exclusively in the *context of B cell activation, not in the context of preventing a T cell mediated autoimmune disorder* (Lederman, col. 11, ll. 18-35). There is no disclosure in Lederman of preventing T cell-mediated autoimmune disease damage in relation to type I diabetes. While Lederman lists diseases that can be treated by his method, most of the diseases listed are known to be primarily B cell-mediated. While diabetes and transplant rejections are included in the list, a fair reading of Lederman is that it merely implies that diabetes mellitus, as well as transplant rejections, have B cell-mediated components that can perhaps be treated by the 5c8 antibody. It was known in the art in June of 1995 that the immune response in both transplant rejections and type I diabetes had both B cell- and T cell-mediated components. *See* Declaration of Clark, ¶ 13. However, nothing in the teachings or disclosure of Lederman suggests that the disclosed method can be used to treat the T cell-mediated aspects of the disease. *See* Declaration of Clark, ¶ 18 and 19. Because these are two completely separate immune responses, in June of 1995, the suggestion to use a method to treat one would not have led a person of skill in the art to even try the same method to treat the other. *See* Declaration of Clark, ¶ 9.

The Examiner, while conceding that Lederman only teaches B cell activation, asserts that it was known in the art that "*CD40L was expressed on important activated CD4+ T cells* that regulated various immune responses and that CD40L was targeted in conditions and disorders know to be cell-mediated at the time the invention was made." *See* Final Office Action dated February 7, 2007, page 9 (emphasis added). The Examiner also states that the prior art teaches "the advantages of anti-CD40L antibodies to inhibit immune responses by targeting the CD40L on T helper cells in therapeutic modalities of immunosuppression at the time the invention was made." *Id.* However, the T cell-mediated response in type I diabetes involves autoreactive CD8+ cytoxic T cells, not CD4+ T helper cells. *See* Clark Declaration, ¶¶ 3 and 14. The disclosure of Lederman that CD40L was expressed on helper T cells would not lead a person of skill in the art to the use of an anti-CD40L antibody in T cell-mediated immune response because these helper T cells are not involved in this response. *See* Declaration of Clark, ¶¶ 3, 12 and 14.

Additionally, Lederman does not even teach a person of skill in the art to treat the B cell-mediated diseases because there are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. There are no data showing the effect of normal human T cells expressing what is called T-BAM on an immune response *in vitro* or *in vivo*. Lederman provides no evidence to establish that: (a) the 5c8 anti-CD40L monoclonal antibody binds to cells other than human T cells activated by non-physiologic stimuli and the Jurkat human T cell line; and (b) the 5c8 antibody can affect an autoimmune disease in an animal including humans. There are no functional data in Lederman using T cells activated with physiologic stimuli, *i.e.*, antigen, and no data assessing the role of an anti-CD40L antibody *in vivo* which would be essential to know if the antibody could inhibit autoimmune disease. *See* Declaration of Clark, ¶¶ 20-24.

For the reasons set forth above, Lederman does not teach or suggest the currently claimed invention of "a method for preventing T cell mediated tissue destruction associated with type I diabetes.. wherein ... tissue destruction results from a T cell mediated immune reaction to autontigen" either alone or in combination with Noelle.

Moreover, the Noelle '037 patent would not have lead a person of skill in the art to treat diabetes with anti-gp39 antagonists, either alone or in combination with other prior art. Noelle discloses a method for inducing antigen-specific T cell tolerance and a means to block allogeneic T cell responses as measured by graft versus host disease (GVHD) using anti-gp39 monoclonal antibodies. One skilled in the art at the time the present invention was made might have thought that this treatment may be pertinent for the treatment of diabetes to the extent that the method in Noelle involves pancreatic allografts (Declaration of Clark, ¶ 17). However, this would not suggest that the underlying disease of diabetes could be directly treated with an anti-gp39 antagonist. Nor was it known in June of 1995 that pancreatic allograft rejection could be treated with anti-CD40L antagonists. In short, the Noelle '037 patent concerns the induction of antigen-specific T cell tolerance that would applicable to allogeneic transplantation or autoimmune disease where the autoantigens are clearly defined. *See* Declaration of Clark, ¶ 17.

More importantly, there would have been no reasonable expectation of success that the claimed invention would work to treat T cell-mediated tissue destruction by following the teachings of the cited prior art references. As discussed fully in the Response filed November 6, 2006 and the accompanying Declaration of Edward Clark, there are two distinct types of immune responses, B cell-mediated, or humoral, and T cell-mediated or cellular. While it was known at the time of the invention that type I diabetes involved both B cell-mediated and T cell-mediated responses, it was not known at the time that gp39 had a role in immune responses other than humoral, *i.e.*, those involving T cell-B cell interactions. Thus, in 1995, one of ordinary skill in the art would not have had a reasonable expectation of success in treating T cell-mediated responses in type I diabetes with an anti-gp39 antibody from these early teachings.

Humoral responses can be transferred from one experimental animal to another by the transfer of antigen-specific antibodies. *See* Declaration of Clark, ¶ 5. In humoral immune responses, binding of antibodies to antigens can target an antigen for phagocytosis, lead to complement fixation and/or attract further inflammatory cells. These mechanisms lead to cellular injury. An example of an antibody mediated disease is systemic lupus erythematosus. *See* Declaration of Clark, ¶ 6.

In contrast to humoral responses, T cell-mediated responses are not controlled by autoantibodies and represent an immune response that is independent of B cell activation. Immune responses of this type can be transferred in experimental models by the transfer of T cells as opposed to antibodies. An example of a T cell-mediated autoimmune disorder model is EAE, an animal model for multiple sclerosis. Another model is the NOD mouse, which spontaneously develops insulitis and diabetes. These diseases can be transferred from one animal to another by the transfer of T cells. *See* Declaration of Clark, ¶ 7, Exhibits B and C to Clark Declaration.

Thus, it can be seen that B cell and T cell-mediated responses are completely different. At the time of the invention, one of ordinary skill in the antibody art would not have recognized that a gp39 antagonist would have an effect on T cell-mediated disease because the response the autoantigen is independent of B cell activation, which was considered the primary role of gp39. *See* Clark Declaration, ¶ 9. It was not known in June of 1995 that gp39 had any role in non-B cell immune responses. *See* Clark Declaration, ¶¶ 9-11, Exhibits D, E, F, and H to Clark Declaration. In fact the first study to even suggest the role of CD40-CD40L in T cell-mediated immune responses was published in November of 1997, almost a year and a half after the invention date. *See* Declaration of Clark, ¶ 15, Exhibit K to Clark Declaration.

The Examiner states that the Applicant is relying upon mechanisms of action of the asserted teachings of the prior art and has not distinguished the expectation of success in treating a patient with diabetes with a gp39/CD40L/5c8 antagonist based upon the teachings of the prior art. *See* Final Office Action dated February 6, 2007, page 7. Applicants respectfully submit it is more than a difference in mechanism of action that distinguishes the present invention over the teachings of the prior art. The treatment of "tissue damage [that] results from a T cell mediated immune reaction to an autoantigen" by a patient with type I diabetes as currently claimed is different than treating tissue damage resulting from B cell mediated immune reactions. It involves treating inflammation and destruction of beta cells by macrophages and cytotoxic T cells, not autoantibodies. As shown, this type of tissue damage was not considered treatable by gp39 antagonists in June of 1995. *See* Declaration of Clark, ¶¶ 14, 16.

Autoimmune diseases are often the products of both B cell- and T cell-mediated responses. But while it would have been expected in June of 1995 to successfully treat the B cell/humoral/antibody-mediated responses using an anti-gp39 antagonist which interferes with the helper T cell-B cell interactions, it would have not been expected that the same method would be useful to treat T cell-mediated aspects of autoimmune disease and T cell-mediated tissue destruction. *See* Declaration of Clark, ¶¶ 9-16. In June of 1995, the art was such that gp39 was thought only to be involved in T cell- B cell interactions. Its potential role in non-B cell immune responses was only elucidated after the filing date of the present application. More importantly, the role of gp39 in the T cell-mediated aspects of diabetes remained untested and unknown at least a year after the filing date of the present application. Thus, one of skill in the art would not have been lead to the presently claimed invention of using an anti-gp39 antibody to treat T cell-mediated tissue destruction in diabetes based upon the teachings in Lederman of antagonists of the helper T cell-B cell interaction. There was simply not enough knowledge in the art at the time. Indeed, the state of the art would have lead a person of skill to the correct conclusion that Lederman only teaches the use of an anti-gp39 antibody in the treatment of B cell-mediated autoimmune disease. Thus, the success of the method of the present invention in treating T cell-mediated tissue destruction is unexpected in light of the knowledge in the art in June of 1995.

Thus, the teachings of Lederman and Noelle, either alone or in combination, do not teach or suggest every claim limitation. Specifically, the cited references do not teach or suggest "a method for preventing T cell mediated tissue destruction associated with type I diabetes ... wherein ... tissue destruction results from T cell mediated immune reaction to an autoantigen." Furthermore, as shown above, the state of the art in June of 1995 was such that the currently claimed invention was unexpected and a person of skill in the art would not have had a reasonable expectation of success in treating T cell-mediated immune responses and tissue damage associated with diabetes based upon the teachings of Lederman and Noelle.

It is also respectfully submitted that the evidence submitted with the April 1, 2005 reply (Noelle Declaration (Exhibit D) and Exhibits B and C) as to the unexpected superior results of the 24-31 antibody *in vivo* as compared to the 5c8 antibody has not been accorded its due weight. In

addition to being therapeutically safe by not causing thomboses (contrary to hu5c8), the antibodies of the presently claimed method block binding of CD40 to gp39 *in vivo* more effectively than 5c8. Due consideration is required of objective evidence of superior results.

In view of the arguments and amendments set forth above, the pending claims are believed to be in condition for allowance and such action is earnestly solicited.

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Respectfully submitted,

By _____

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